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Expectant Management of Stage A-1 (T1a) Prostate Cancer Utilizing Serum PSA Levels: A Preliminary Report

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Background and Objectives: The natural history of stage A-1 (T1a) prostate cancer remains unpredictable. Although stage A-1 (T1a) was traditionally considered an indolent lesion, recent reports have documented the potential progression of stage A-1 (T1a) cancer.
Methods: Eight men aged 65 to 76 years at the time of diagnosis with stage A-1 (T1a) prostate cancer received no therapy. These men have been followed from 3 to 9.5 years (mean, 6.25 years). During this period, the patients have been followed with periodic rectal examinations and prostate-specific antigen (PSA) levels.
Results: The PSA levels of five of the eight patients remain in the normal range and no patient has had a change in his rectal examination. In the three patients who had elevated PSA levels, there was no evidence of metastatic disease. No patient has died from prostate cancer; one patient died from cerebrovascular causes.
Conclusions: Patients with stage A-1 (T1a) prostate cancer have an unpredictable natural history. PSA levels can be used to monitor disease progression and identify those patients where observation is no longer appropriate. *J. Surg. Oncol. 1999:70:49–53.* © 1999 Wiley-Liss, Inc.

KEY WORDS: prostate-specific antigen; stage A-1 prostate cancer; conservative management

INTRODUCTION

The management of patients with stage A-1 prostate cancer remains controversial among physicians. This is due in large part to the fact that the definition of stage A-1 prostate cancer has not been consistent in the literature and that only a few studies have followed untreated patients with stage A-1 disease in the long-term. Therefore, the natural history of stage A-1 cancer of the prostate is not well understood.

Whitmore [1] first divided prostate cancer into stages A, B, C, and D in 1956 and Jewett [2] later subdivided stage A into A-1 (focal, low-grade disease) and A-2 (diffuse, high-grade disease). Generally speaking, most urologists today define A-1 prostate cancer as occurring in those patients where cancer is present in less than 5% of the pathologic specimen and where all the tumor present is histologically well or moderately differentiated. In the UICC (TNM) classification, stage A-1 is classified as T1a [3].

Correa et al. [4] reported the first large series that reviewed patients with stage A-1 prostate cancer. They identified 39 patients with stage A-1 disease: 2 patients underwent total prostatectomy, 17 patients were given hormonal therapy (1-mg stilbestrol q.d.), and 20 patients were observed. Although the study is somewhat vague and does not always clearly differentiate between those patients who received hormonal therapy and those who were observed, the conclusion of the study is that focal, well-differentiated prostate cancer is an indolent disease

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TABLE I. Stage A-1 (T1a) Prostate Cancer Patient Characteristics

Patient number	Age diagnosed (years)	Gleason score	Restaging studies	Current status
1	65	3	None	Alive; no evidence of progression 9.5 years after diagnosis
2	73	4	None	Died of cerebral hemorrhage 6 years after diagnosis of prostate cancer
3	68	3	None	Alive; no evidence of progression 6 years after diagnosis
4	73	7	Bone scan negative ×3 Repeat prostate biopsy negative ×3 Abdominal CT scan negative ×1	Alive; PSA has increased from 10.6 to 46.0, but no radiographic or clinical signs of progression
5	76	5	None	Alive; no evidence of progression 6 years after diagnosis
6	74	3	None	Alive; no evidence of progression 8 years after diagnosis
7	76	4	None	Alive; no evidence of progression 3 years after diagnosis
8	71	3	None	Alive; no evidence of progression 6 years after diagnosis

and can be observed. No patient in their series died from prostate cancer, with follow-up to 10 years.

In 1977, Heaney et al. [5] reviewed their experience with 100 patients with stage A disease. Using the histologic criteria mentioned above, 46 patients were identified as having stage A-1 disease. All of these 46 patients with stage A-1 disease were followed for 10 years or more and 3 were found to have residual or recurrent cancer and only 1 patient actually died of the disease. However, about half of their patients received hormonal therapy or surgery. Nonetheless, their data would also support the indolent nature of stage A-1 disease. In 1981, Cantrell et al. [6] reported on 47 patients who fulfilled the pathologic criteria for stage A-1 disease. Of these patients, followed from 2 to 17 years, only one patient demonstrated progression of disease and no patient died from prostate cancer.

However, more recent reports by Epstein et al. [7], Blute et al. [8], and Zhang et al. [9] showed progression rates of 16%, 27%, and 10%, respectively, in patients with stage A-1 disease. This has caused physicians to reassess the indolent nature of A-1 disease and to advocate radical prostatectomy in some patients.

However, all six of these series [4–9] were published before the routine, widespread use of prostate-specific antigen (PSA) as a prostate cancer marker [10–12]. We therefore utilized serial PSA levels to monitor patients with stage A-1 disease who were being observed without any treatment.

MATERIALS AND METHODS

Eight men, aged 65 to 76 years, underwent a transurethral resection of the prostate for obstructive urinary symptoms. The surgeries were performed from 1983 to 1991 and only three patients (patients 2, 3, 7) had a preoperative PSA level drawn. These three patients had slightly elevated PSA levels: 5.4, 8.4, and 6.6 ng/ml (Hybritech Assay, San Diego, CA), respectively. Preoperative rectal examinations on all the patients were normal. The pathology revealed that all eight patients had low-volume disease (<5% of the resected specimen). Six patients had well-differentiated prostate cancer (Gleason score, 2–4) and two patients had moderately differentiated prostate cancer (Gleason score, 5–7). Metastatic work-ups in all patients were negative.

RESULTS

Treatment options were discussed with the patients. All eight patients elected no treatment, either because of age, comorbidities, or the patient's desire to defer any initial invasive therapies. All patients were followed with regular office appointments, at which time a PSA was drawn and a rectal examination performed. The patient characteristics are shown in Table I. The sequential PSA levels over time are displayed in Figure 1.

Of the three men (patients 3, 4, 6) who exhibited a significant rise over their baseline PSA, two had no repeat metastatic work-up performed because of age or associated comorbidities. Patient 4 had a rise in his initial PSA from 10.6 to 46.0 ng/dl over a 7-year period. During his follow-up, because of the rising PSA, three subsequent prostate biopsies revealed no tumor. Three additional bone scans and one abdominal CT scan were done periodically during the course of his follow-up and none revealed metastatic disease. He remains asymptomatic over 7 years following his surgery.

DISCUSSION

Previously there have been no clearly defined guidelines for management of patients with stage A-1 disease. However, there are published reports that look at three major therapeutic options: repeat transurethral resection of the prostate (TURP), radical prostatectomy, and observation alone.

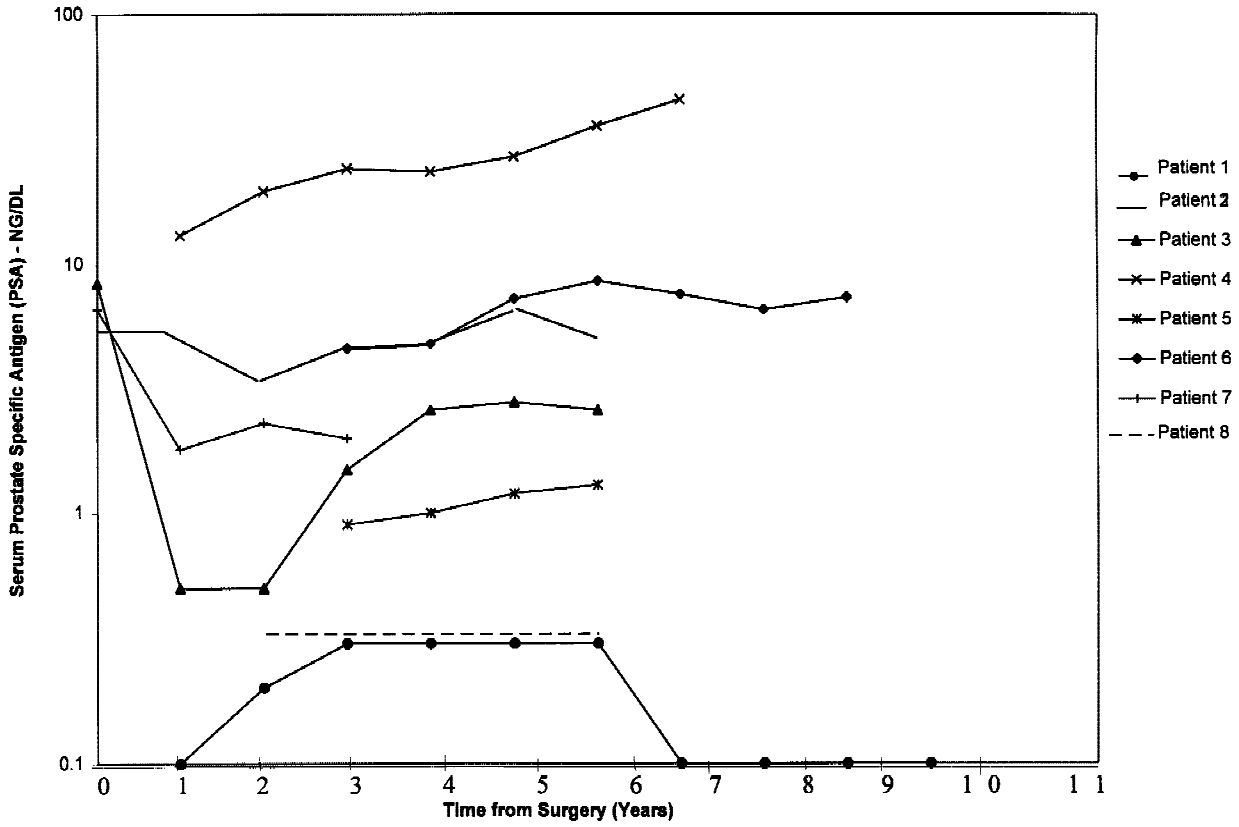

Fig. 1. Sequential PSA levels of patients observed with stage A-1 prostate cancer.

TABLE II. Repeat Transurethral Resection of the Prostate (TURP) in Patients With Stage A-1 Prostate Cancer

	Total patients	No tumor (%)	A-1 (%)	A-2 (%)
Zhang et al. [9]	52	38 (73.1)	14 (26.9)	0 (0.0)
McMillen et al. [13]	27	17 (63.0)	3 (11.1)	7 (25.9)
Parfitt et al. [14]	55	45 (81.8)	8 (14.5)	2 (3.6)
Bridges et al. [15]	40	28 (70.0)	10 (25.0)	2 (5.0)
Kopper et al. [16]	61	49 (80.3)	5 (8.2)	7 (11.5)
Sonda et al. [17]	31	22 (71.0)	6 (19.4)	3 (9.7)
Carroll et al. [18]	42	32 (76.2)	7 (16.7)	3 (7.1)
Total	308	231 (75.0)	53 (17.2)	24 (7.8)

Repeat TURP

The rationale for a repeat TURP is to determine if the initial TURP has understaged the tumor either by volume or by grade. The first published study by McMillen and Wettlaufer [13] in 1976 reported a 26% (7 of 27 patients) frequency of tumor upstaging to stage A-2. However, subsequent reports [9,14–18] have shown that although approximately 25% of patients undergoing repeat TURP may demonstrate residual tumor, only about 8% of the patients will actually be upstaged. The results of the seven largest repeat TURP series in the literature are summarized in Table II.

Epstein et al. [19] provide additional data suggesting that the residual tumor found in radical prostatectomy specimens removed for stage A-1 disease was predominantly in the peripheral zone and would be unlikely to have been detected during a repeat TURP. The cumulative experience in the literature would suggest that the yield of a repeat TURP in stage A-1 disease is low and should not be done routinely unless there is reason to suspect that the patient will be upstaged.

Radical Prostatectomy

As urologists have become more familiar with the technique of anatomic radical prostatectomy, an increasing number of patients with stage A-1 disease are being

TABLE III. Natural History of Stage A-1 Prostate Cancer

	Number of patients	Therapy	Cancer progression (%)	Cancer death (%)	Follow-up (years)
Correa et al. [4]	39	None or endocrine	3/39 (7.7)	0/39 (0)	0–10
Heaney et al. [5]	46	None or endocrine	3/46 (6.5)	1/46 (2.2)	10
Cantrell et al. [6]	48	None	1/48 (2.1)	0/48 (0)	4
Epstein et al. [7]	50	None	8/50 (16.0)	6/50 (12.0)	8
Blute et al. [8]	15	None	4/15 (26.7)	0/15 (0)	10–25
Zhang et al. [9]	132	None	13/132 (9.8)	0/132 (0)	5–23
Total	330		32/330 (9.7)	7/330 (2.1)	

considered as candidates for radical prostate surgery. Larsen et al. [20] have reported on 64 patients, aged 46 to 70 years, who underwent radical prostatectomy for apparent stage A-1 disease. Their findings revealed 6% of the specimens with no residual tumor, 74% with minimal cancer, and 20% with substantial cancer. Zincke et al. [21] reported on 32 patients, aged 38 to 74 years, who underwent radical prostatectomy for clinical stage A-1 disease. In their series, 25% of the patients had no tumor in the specimen, 41% had minimal disease, and 34% had extensive disease. In view of these findings, both groups of authors recommended radical prostatectomy for young men with clinical stage A-1 prostate cancer.

Observation Alone

As mentioned previously, there have been six published series that have examined the natural history of untreated stage A-1 prostate cancer. All of these series predated the routine use of PSA in the management of prostate cancer. These six series demonstrate a cumulative cancer progression rate of 9.7% and a cancer death rate of 2.1% (Table III).

In view of these data, it would appear that some patients, especially those who are older or with comorbidities can be followed without treatment. The dilemma has been how to predict and detect progression. Prostate specific antigen provides the urologist with the most sensitive modality to detect disease progression in prostate cancer.

Prostate-specific antigen has markedly enhanced our ability to diagnose and stage prostate cancer [10–12]. At the present time, there is no accurate way to predict the natural history of an individual prostate cancer. Clearly, although many stage A-1 prostate cancers will remain indolent, some have the potential to progress. Treatment options are influenced by patient age, comorbidities, and patient wishes.

In the group of patients who elect observation, serial prostate-specific antigen levels along with regular rectal examinations appear to be the most reliable means to monitor tumor progression. Using this strategy, we have followed eight men for a mean of 6.25 years. During this period, three men had significant increases in their serum PSA (patients 3, 4, 6). Because of age and comorbidities, patients 3 and 6 were not restaged. Patient 4 was rebiopsied and restaged without evidence of disease progression. No patient has died of prostate cancer during the study period.

Our preliminary experience would suggest that prostate-specific antigen monitoring adds a valuable dimension to follow patients with stage A-1 prostate cancer who elect no treatment. If the PSA rises significantly, the patient may be restaged and the need for more aggressive treatment reassessed.

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